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Cushing's Disease in a 7-Month-Old Girl due to a Tumor Producing Adrenocorticotropic Hormone and Thyreotropin-Secreting Hormone

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Key Words
Pituitary adenoma · Adrenocorticotropic hormone · Thyreotropin-secreting hormone · Cushing's disease · Cushing's syndrome · Neurosurgery

Abstract
We present the case of a 7-month-old baby with Cushing's disease due to an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma combined with cells producing thyreotropin-secreting hormone (TSH). In MRI scans, a contrast-enhancing lesion was seen inside the pituitary fossa, and it extended into the suprasellar region. On the assumption of a pituitary adenoma, surgery was performed. Corresponding with biochemical findings, histopathological evaluation revealed an ACTH- and TSH-producing tumor. Genetic analysis did not demonstrate an alteration at codon 201 (Arg) and 227 (Glu). To our knowledge, this is the first case described in a child of this age.

Introduction

Brain tumors account for 18.6% of malignant neoplasms and 40–50% of all solid tumors in childhood [1]. The incidence is 4–5 cases per 100,000 children per year. However, there is considerable variation between type and tumor location [2]. Approximately 55% of intracranial tumors are located in the posterior fossa. Only 5–7% of supratentorial lesions are located in the sellar and parasellar area, most of them are craniopharyngiomas [3].

In adults, out of one million inhabitants only one will develop an adrenocorticotropic hormone (ACTH)-producing adenoma of the pituitary gland. There are no statistical data for the incidence of pituitary adenomas in childhood. Only few cases are known. We describe the case of a 7-month-old girl with Cushing's disease due to an ACTH-secreting pituitary adenoma combined with cells producing thyreotropin-secreting hormone (TSH). To our knowledge and in review of the literature, this is the first case described.

Case Report

We present the case of a 7-month-old baby, the twin of a normal sister and healthy parents. Five months after birth, the parents noticed progressive obesity and fatigue. The baby was less active, did not fixate on objects and frequently cried. The mother presented the baby to an ophthalmologist who diagnosed a papilledema and recommended neurosurgical evaluation.

Physical Examination

On admission the child showed diminished vigilance with reduced spontaneous movements. Compared to her twin sister (6.5 kg) a weight gain of 1 kg was noticed. The examination revealed typical

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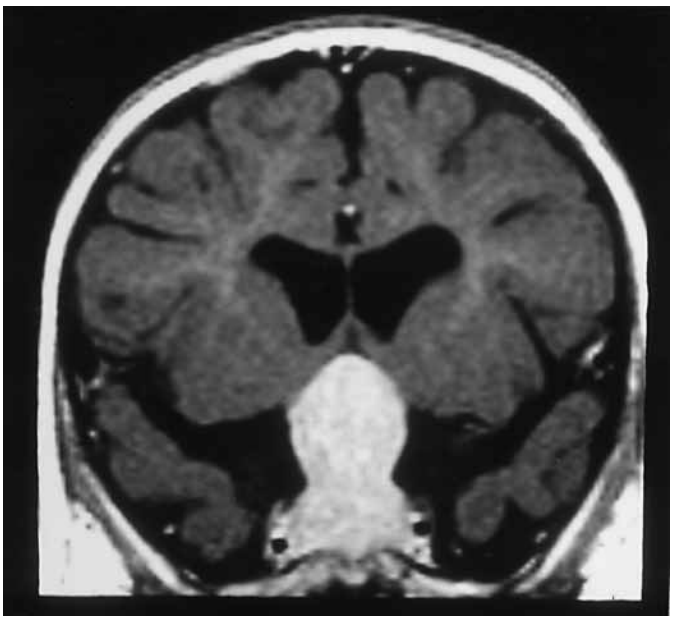

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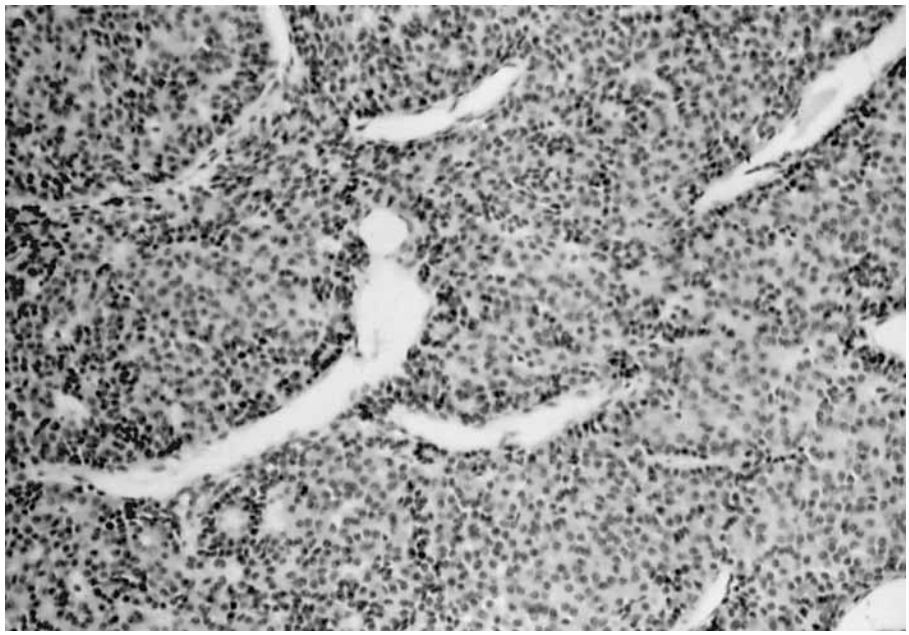
Fig. 1, 2. Magnetic resonance imaging of the pituitary adenoma. T_1-weighted coronal (**1**) and sagittal (**2**) showing a 2 × 2 × 3 cm measuring, contrast enhancing lesion with intra- and suprasellar extension.

Fig. 3, 4. Postoperative coronal (**3**) and sagittal (**4**) MRI-slices. Complete tumor removal using a pterional approach.

cushingoid features including a moon face, truncal obesity and buffalo hump. There were no clinical signs and symptoms of hyperthyroidism. Otherwise, the physical evaluation was normal including skin development and pigmentation.

Biochemical Investigations

Preoperatively, morning blood cortisol was initially 1,002 nmol/l (normal value, NR: 80–630 nmol/l); the ACTH value was moderately elevated (24.1 pmol/l, NR: 3.5–4.9 pmol/l). Prolactin, human growth hormone (HGH), aldosterone, insulin-like growth factor 1 (IGF-1) and human chorionic gonadotropin were within physiological limits. Testosterone could not be detected. Basal TSH was 1.28 mU/l (NR: 0.35–4.00 mU/l). After stimulation with TRH, a normal increase in TSH up to 8.16 mU/l was found. Blood count and serum electrolytes showed normal values.



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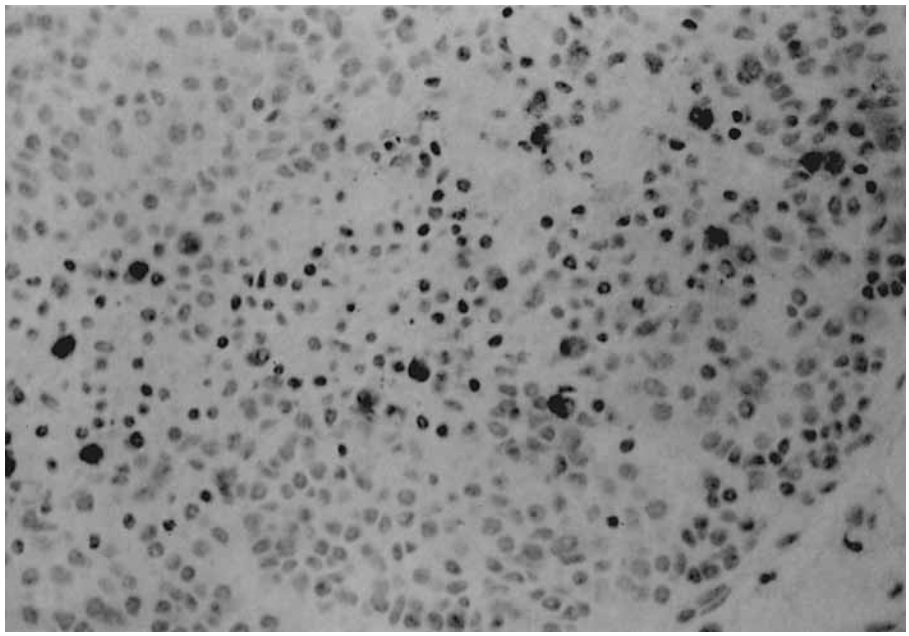

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Fig. 5, 6. Histopathological and immunohistological evaluation showed tumor cells with irregular nuclei and chromatin filling. The cytoplasma stained weakly for a basophilic or eosinophilic compound (**5**). TSH and ACTH antibodies were positive in up to 5% of tumor cells (**6**).

Radiographs and MRI Scans

Plain X-ray films of the skull showed an excavated sella turcica T_2-weighted magnetic resonance images presented an intra- and suprasellar isointense lesion measuring 2 × 2 × 3 cm. In the T_1-weighted scans, hypo- and hyperintense plaques were seen. After application of gadolinium, a contrast-enhancing lesion inside the pituitary fossa was identified that extended into the suprasellar region. The optic chiasma and prechiasmatic parts of the optic nerves were compressed by the tumor. Parts of the mass lesion surrounded both internal carotid arteries. The differential diagnosis included a pituitary tumor or an optic glioma (fig. 1–4).

Surgical Treatment

On the assumption of a pituitary adenoma, surgery was performed. A pterional approach was selected because of the patient's age and the suprasellar extension of the lobulated tumor. Intraoperatively, the optic nerves and internal carotid arteries were exposed. The tumor compressed and displaced the optic chiasm and led to an elongation of the optic nerves. The tumor was completely removed, leaving the nerves and vessels unaffected.

Histopathological Evaluation

Solid tissue with rosettes and tubular structures was found. The tubular cell components consisted of spherical, protein content and

calcification similar to Crooke's hyaline. Tumor cells showed irregular nuclei with chromatin filling. The cytoplasm did not show a strong basophilic or eosinophilic compound. Immunohistological staining with TSH and ACTH antibodies was positive in up to 5% of tumor cells. No expression of follicle-stimulating hormone, luteinizing hormone (LH), prolactin or HGH was found (fig. 5, 6).

The histopathological evaluation was in accordance with a pituitary adenoma with low quantities of ACTH and TSH secretion.

Genetic Analysis

Point mutations of the α-subunit of GTP-binding proteins ($G_s\alpha$) are related to the development of growth hormone (GH)-secreting pituitary adenomas in 30–45% of adult patients [4]. We examined the child's tumor DNA in order to assess a relationship between the ACTH-secreting adenoma and $G_s\alpha$ mutations. DNA was prepared using standard techniques of cell lysis and DNA separation. PCR cycles were carried out with following primer pairs: exons 7–8 (466 bp) 5′-TGAGCCTGACCTTGTAGAGAGACACA-3′ and 5′-GGTTATTCCAGAGGGACTGGGGTGAA-3′, as well as exons 9–11 (698 bp) 5′-GACATTCACCCCAGTCCCTCTGGAAT-3′, respectively, 5′-AGAACCACCGCAATGAACAGCC-3′ and exons 7–10 5′-GCGCTGTGAACACCCCACGTGTCT-3′ and 5′-CGCAGGGGGTGGGCGGTCACTCCA-3′.

No alterations at codon 201 (Arg) and 227 (Glu) were detected. The results correspond with the gsp-negative findings in children with GH-producing tumor cells [5].

Postoperative Course and Follow-Up

The child rapidly recovered from the surgical intervention. A cerebrospinal fluid leak had been treated by wound reinforcement. Six weeks after tumor removal, no ACTH production was detectable. Four days after surgery, a very low TSH of 0.04 mU/l in the presence of low normal levels of peripheral thyroid hormones (triiodothyronine 1.26 nmol/l, NR: 1.10–3.20 nmol/l; tetraiodothyronine 94 nmol/l, NR: 60–160 nmol/l) were detected, suggesting secondary hypothyroidism. Cortisol and thyroxin had to be substituted. Other hormones of the anterior lobe of the pituitary and adrenal glands such as HGH (0.25–0.42 ng/ml), aldosterone (209–484 pmol/l) and IGF-1 (14.0 ng/ml), were decreased, indicating temporary insufficient pituitary production.

At the 1-year follow-up the child was still behind her twin sister in neurological development. Her vision was still partly impaired, and the baby's weight corresponded to the chronological age.

Discussion

To our knowledge, this is the first case report on a child of this age with a combined ACTH- and TSH-producing pituitary adenoma. In 70% of pediatric patients, endogenous Cushing's syndrome is caused by adrenal tumors with a distinct female predominance, and they are mostly due to pituitary adenomas. Cushing's disease affects children of all ages [6]. However, after the age of 7 years, pituitary tumors are the primary reason for development of Cushing's syndrome, and the sex difference disappears [7, 8].

Other causes are exceedingly rare, including primary pigmented nodular adrenocortical disease (PPNAD) of the adrenal glands and ectopic ACTH production by a nonpituitary tumor [6, 9–14].

Houwen et al. [7] presented 4 young patients between 5 and 14 years with Cushing's disease related to ACTH overproduction caused by PPNAD. A study by Thomas et al. [9] described 2 out of 18 children with Cushing's syndrome who developed a secondary pituitary tumor induced by bilateral nodular dysplasia. Though they are in second place after adrenal tumors in inducing cortisol overproduction, ACTH-secreting pituitary lesions are rare in childhood. In a 33-year survey, 10 children, aged 1–7 years, were reported with hypercortisolism due to pituitary adenomas [8]. No additional hormone overproduction was documented. Maeder et al. [15] presented the CT and MRT findings of a 12-month-old girl with a large tumor arising from the sella turcica. The histology revealed an ACTH-secreting pituitary adenoma.

The coincidence of ACTH-producing pituitary adenomas with additional hormone release in childhood has been reported in only a few cases. Puchner et al. [16] treated a 10-year-old boy by surgery. A corticotropin-releasing hormone-secreting intrasellar gangliocytoma combined with an ACTH-producing pituitary tumor was removed. A case report by Faggiano et al. [17] described sexual precocity in a 4.5-year-old boy due to hypersecretion of LH and prolactin. In our patient, the immunohistochemical staining of tumor cells for TSH was not reflected by an elevation of serum TSH or clinical signs of hyperthyroidism, suggesting that only a minority of tumor cells actually secreted TSH.

The symptoms and clinical findings are similar in both children and adults. In our case the leading symptoms were loss of activity and fixation, requiring surgical intervention.

Pituitary tumors may occur as part of the Carney complex, familial multiple neoplasia and lentiginosis syndrome. In the presented child, there was no clinical evidence for the Carney complex [18], as myxomas, spotty pigmentation and schwannomas were missing. The parents were healthy, hence an inherited disorder seemed to be unlikely. GH-secreting pituitary adenoma can express a $G_s\alpha$ mutation in adult patients [4]. In children, one study showed $G_s\alpha$ modifications. Activating sites are found at codon 201 (Arg) and 227 (Glu) of exons 8 and 9, producing the gsp oncogene [5]. Genetic analysis of the child's DNA did not show oncogene mutations of the $G_s\alpha$ gene.

The postoperative course was typical for a complete removal of an ACTH-producing adenoma. Weight reduction could be seen, and cortisone substitution was necessary. Follow-up MRI scans did not identify any residual tumor masses. In the 1-year postoperative observation period, the child's development was still delayed.

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